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(54) **Macroporous and highly resorbable apatitic calcium-phosphate cement**

(57) The present invention is directed to a novel cement powder comprising an organic component consisting of one or more biocompatible and bioresorbable polymers and an inorganic component consisting of one or

more calcium phosphate compounds. The invention also relates to the apatitic CPC resulting from the mixing of said cement powder with a liquid phase and setting.

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DescriptionField of invention

- 5 **[0001]** The invention relates to a macroporous and highly resorbable apatitic calcium-phosphate cement with a high compressive strength useful as bone cement.

Background of invention

- 10 **[0002]** Bone is a composite of biopolymers, principally collagen, and an inorganic component identified as carbonate hydroxyapatite, approximated as $(\text{Ca}, \text{Mg}, \text{Na}, \text{M})_{10}(\text{PO}_4, \text{CO}_3, \text{HPO}_4)_6(\text{OH}, \text{Cl})_2$.

- [0003]** To date, a wide variety of implant materials have been used to repair, restore, and augment bone. The most commonly used implants include autologous bone, synthetic polymers and inert metals. Protocols using these materials have significant disadvantages that can include patient pain, risk of infection during operations, lack of biocompatibility, cost, and the risk that the inserted hardware can further damage the bone. Therefore, a major goal of biomaterial scientists has been to develop novel bone substitutes that can be used as alternatives to these conventional techniques for skeletal repair.

- 15 **[0004]** Bone cements, such as cements based on polymethylmethacrylate (PMMA) offer certain advantages in avoiding the use of solid implants, but also have several disadvantages. Methacrylates and methacrylic acid are known irritants to living tissues, and when PMMA-based cements are cured in vivo, free radicals are generated, which can damage surrounding tissues. Moreover, the polymerization reaction for these materials is highly exothermic, and the heat evolved during curing can damage tissues.

- [0005]** The concept and potential advantages of an apatitic or calcium phosphate cement (CPC) as a possible restorative material was first introduced by LeGeros et al in 1982 ("Apatitic Calcium Phosphates : Possible Restorative Materials", J Dent Res 61(Spec Iss):343).

- 20 **[0006]** There are presently several CPC commercial products. CPC have the following advantages: malleability allowing them to adapt to the defect's site and shape. The introduction of injectable calcium phosphate cements greatly improved the handling and delivery of the cements and opened up areas of new applications for the CPC.

- [0007]** CPC systems consist of a powder and a liquid component. The powder component is usually made up of one or more calcium phosphate compounds with or without additional calcium salts. Other additives are included in small amounts to adjust setting times, increase injectability, reduce cohesion or swelling time, and/or introduce macroporosity.

- 30 **[0008]** The liquid component may consist of one or more of the following: saline, deionized water, dilute phosphoric acid, dilute organic acids (acetic, citric, succinic acid), sodium phosphate (alkaline or neutral), sodium carbonate or bicarbonate, sodium alginate, sodium bicarbonate, sodium citrate, and/or sodium chondroitin sulphate.

- 35 **[0009]** The currently available commercial CPCs suffer from some shortcomings such as absence of macroporosity, slow rate of bioresorbability and a fragile compressive strength. This leads to dangerous stress fractures.

- [0010]** Macroporosity is of great importance for bone regeneration as it facilitates bone cells colonisation of the material, angiogenesis, tissue ingrowth and reabsorption of the material.

- [0011]** Several methods of introducing macroporosity in CPCs have been disclosed.

- 40 **[0012]** One of them consists of liberation of CO_2 during the reaction of acid and NaHCO_3 in providing acid (citric acid) and NaHCO_3 or adding acidic sodium phosphate (NaH_2PO_4) solution to NaHCO_3 .

- [0013]** Other methods have been recommended as introduction of resorbable fibers, e.g. polygalactin ; addition of soluble salts (e.g. calcium chloride and sodium or potassium hydroxide ; addition of pore forming agents (e.g., sugar, NaHCO_3 , calcium salts) ; using frozen sodium phosphate (NaH_2PO_4) solution particles.

- 45 **[0014]** WO2006030054 suggests foaming of a calcium phosphate cement with the addition of surface active agents and the mechanical beating or stirring of same to form air bubbles providing microporosity.

Summary of invention

- 50 **[0015]** Briefly, therefore, the present invention is directed to a novel cement powder comprising an organic component consisting of one or more biocompatible and bioresorbable polymers and an inorganic component consisting of one or more calcium phosphate compounds. Preferably, after mixing with a liquid phase and setting, this cement yields to an apatitic calcium phosphate cement with a macroporosity above 100 μm and a compressive strength above 10 MPa. The cement powder according to the invention is useful as a bone cement.

- 55 **[0016]** The inorganic component precipitates after dissolution in the liquid phase in a calcium-deficient apatite. This thus obtained apatite is degraded by chemical and cellular processes favoured by microporosity.

- [0017]** The polymers of the organic component swell in contact with the liquid phase. After setting, the polymers are integrated in the mineral part. They act as a binder between mineral particles and confer the biomechanical rheological

and elastic properties to the CPC. Their further degradation results in tunnels and macropores interconnected. Inter-connected macropores in the apatitic cement allow its passive resorption by dissolution through the biological fluids and its active resorption through the colonisation of the macropores by osteoclasts.

[0018] The invention also relates to the apatitic CPC resulting from the mixing of said cement powder with a liquid phase and setting. This CPC according to the invention has macroporosity not exhibited by currently disclosed apatitic CPCs and a high compressive strength. These properties confer particular advantages as a high rate of resorbability and an elasticity very close to natural bones.

[0019] The CPC according to the invention can be used for dental and medical applications relating to bone repair, augmentation, reconstruction, regeneration, and osteoporosis treatment, and also for drug delivery, and as scaffolds for tissue engineering. Other potential dental applications are : repair of periodontal defects, sinus augmentation, maxillo-facial reconstruction, pulp-capping materials, cleft-palate repair, and as adjuvants to dental implants. Additional medical applications include repair of large bony defects, repair of bone fractures caused by trauma, or associated with osteoporosis ; for spine fusion, surgery revision, bone augmentation, and for bone reconstructions associated with cancer therapy.

Definitions

[0020] "Biocompatible" used herein means well tolerated by the host organism and which does not cause rejection reaction, toxic reaction, noxious lesion or noxious effect on its biological functions.

[0021] As used herein, a "bioresorbable polymer" is a polymer whose degradative products are metabolized in vivo or excreted from the body via natural pathways.

[0022] An "apatitic" calcium phosphate cement crystallises in the hexagonal system having the formula $\text{Ca}_{5x}(\text{PO}_4)_3x, (\text{OH}, \text{Cl}, \text{F})_x$ with $x \geq 1$.

[0023] A calcium phosphate is said "amorphous" without crystalline structure.

[0024] A "macropore" is a pore with a diameter above 100 μm . The "macroporosity" is the state of cement which contains macropores with a diameter above 100 μm , preferably between 100 and 300 μm .

[0025] A "macroporosity above 200" means that the macropores of the cement have in average a diameter above 200 μm .

[0026] The "compressive strength" is the maximal compressive stress supported by the cement sample upon failure. It is expressed in MPa [Mnewtons/m²].

[0027] "Setting" of a cement means hardening of a cement.

[0028] An "injectable cement" means a cement sufficiently fluid to flow through a needle with a diameter of a few millimetres, preferably between 1 and 5 mm.

[0029] A "microparticle" has a diameter less than 1 mm.

[0030] A "microsphere" of polymer is a microparticle formed by a homogenous polymeric matrix with a diameter less than 1 mm, preferably between 100 and 300 μm , preferably 150 and 250 μm .

[0031] A "microcapsule" of polymer is a hollow microsphere constituted by a polymeric envelope surrounding a reservoir with a diameter less than 1 mm, preferably between 100 and 300 μm , preferably 150 and 250 μm .

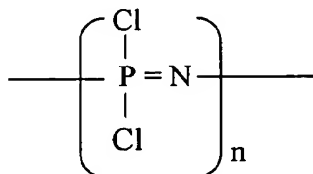
[0032] An "implant" is an object introduced in the body to replace in part or entirely a tooth, a joint, a bone or a cartilage.

[0033] A "minimally invasive surgery" means a technique of surgery that does not require a large incision but a few centimetres incision, preferably ≤ 5 cm.

[0034] Dendrimers are high size arborescent (dendritic) polymers produced by iterative processes from one molecule with at least three reactive sites.

[0035] Polysaccharids are a class of carbohydrates, such as starch and cellulose, consisting of a number of monosaccharides joined by glycosidic bonds.

[0036] Polyphosphazenes have the general following formula



with $n > 1$.

Detailed description of invention

[0037] The first object according to the invention consists in a cement powder comprising an organic component consisting of one or more biocompatible and bioresorbable polymers and an inorganic component consisting of one or more calcium phosphate compounds. This powder cement sets with a liquid phase in an apatitic calcium phosphate cement with a macroporosity above 100 μm , preferably between 100 and 300 μm , most preferably between 200 and 300 μm and a compressive strength above 10 MPa, preferably above 20 MPa, most preferably above 25 MPa.

[0038] Preferably, this compressive strength is achieved with an amount of polymer in the cement powder between 0.1 and 30%, preferably 2 and 30%.

[0039] This macroporosity is achieved with the degradation of the polymer microparticles integrated in the mineral part after setting. Preferably, the appropriate diameter of the polymer microparticles is between 20 and 300 μm , more preferably 50 and 250 μm , the most preferably 100 and 200 μm .

[0040] Biocompatible and bioresorbable polymers useful in the invention include, for example, a polymer from the linear polyester family, such as polylactic acid, polyglycolic acid or polycaprolactone and their associated copolymers, e.g. poly (lactide-co-glycolide) at all lactide to glycolide ratios, and both L-lactide or D,L-lactide; polyphosphazenes, dendrimers and polysaccharides; polyorthoester, polyanhydride, polydioxanone, hyaluronic acid and polyhydroxybutyrate and their salts and mixtures thereof.

[0041] Polyphosphazenes, dendrimers, polysaccharides and their salts and mixtures thereof are preferred as the organic component of the cement powder according to the invention. In addition to their physical properties and good compressive strengths, these can be produced with appropriate resorption speed, hydrophilic properties and solubility. Then, this allows the control of their resorbability and the guided resorption-substitution of the CPC.

[0042] Polyphosphazenes which can be used according to the invention are preferably selected from the group consisting of poly(ethyl oxybenzoate)phosphazene (PN-EOB), poly(propyl oxybenzoate) phosphazene (PN-POB), poly[bis(sodium carboxylatophenoxy)phosphazene] (Na-PCPP), poly[bis(potassium carboxylatophenoxy) phosphazene] (K-PCPP), poly[bis(ethyl alanato)phosphazene] (PAaP), poly[bis(carboxylatophenoxy)phosphazene] (acid-PCPP), and their salts and mixtures thereof.

[0043] Polysaccharides which can be used according to the invention are preferably cellulose ethers, more preferably selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC).

[0044] Biocompatible and bioresorbable polymers according to the invention can be used as fine powders, fibers or microparticles. Polymer microparticles can be microspheres or microcapsules, preferably encapsulating one or several excipients such as saccharose, glucose, water, a gas as air, or one or several pharmaceutically active substances as an antibiotic, an anti-inflammatory drug, an anti-cancer drug, a drug against osteoporosis, a growth factor or a mixture thereof. Encapsulating methods are well known by the one skilled in the art.

[0045] The organic component varies between 0.1 to 30% by weight of the total amount of the cement powder according to the invention.

[0046] Preferably, the ether cellulose amount varies between 0.1 to 2 or 3% by weight of the total amount of the cement powder according to the invention.

[0047] Calcium phosphate compounds useful in the invention include amorphous calcium phosphate (ACP), $\text{Ca}_x(\text{PO}_4)_y \cdot \text{H}_2\text{O}$; monocalcium phosphate monohydrate (MCPH), $\text{CaH}_4(\text{PO}_4)_2 \cdot \text{H}_2\text{O}$; dicalcium phosphate dihydrate (DCPD), $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$, also called brushite; dicalcium phosphate anhydrous (DCPA), CaHPO_4 ; precipitated or calcium-deficient apatite (CDA), $(\text{Ca}, \text{Na})_{10}(\text{PO}_4, \text{HPO}_4)_6(\text{OH})_2$; alpha- or beta- tricalcium phosphate (α -TCP, β -TCP), $\text{Ca}_3(\text{PO}_4)_2$; and tetracalcium phosphate (TTCP), $\text{Ca}_4\text{P}_2\text{O}_9$.

[0048] Easily resorbable calcium phosphate compounds are preferred.

[0049] An inorganic component consisting of one or more calcium phosphate compounds selected from the group consisting of α -TCP, β -TCP, ACP, MCPH, DCPA and mixtures thereof, is preferred.

[0050] An inorganic component comprising α -TCP is more preferred. α -TCP has the formula $\alpha\text{-Ca}_3(\text{PO}_4)_2$. α -TCP is easily transformed in calcium-deficient hydroxyapatite (CDA) in aqueous solution. This property is used to form apatitic CPCs.

[0051] An inorganic component including α -TCP and ACP is particularly preferred. ACP is the most soluble in the group of calcium phosphate compounds used in many CPCs. ACP can be made more or less stable (i.e. more or less soluble or more or less susceptible to transform to other calcium phosphates) depending on the ions incorporated in it. (LeGeros et al., (1973), "Amorphous calcium phosphates:synthetic and biological").

[0052] The most preferred inorganic component according to the invention consists of α -TCP and ACP.

[0053] The inorganic component can also comprise strontium (Sr), magnesium (Mg), gallium, or sulphates ions. For example, strontium nitrate $\text{Sr}(\text{NO}_3)_2$ are used. The addition of these ions allows to better control setting and to improve dissolution of the final product.

[0054] A second object according to the invention is an apatitic calcium phosphate cement as the final product resulting from the mixing between a cement powder according the invention, that is comprising an organic component consisting

of one or more biocompatible and bioresorbable polymers and an inorganic component consisting of one or more calcium phosphate compounds, and a liquid phase and setting. A CPC according to the invention has a macroporosity above 100 μm , preferably between 100 and 300 μm , most preferably between 200 and 300 μm and a compressive strength above 10 MPa, preferably above 20 MPa, most preferably above 25 MPa.

[0055] The inorganic component of the CPC allows an intimate bond with the native bone and osteogenic properties. The organic component allows macroporosity interconnected in the mineral matrix and improves the cohesion, the elasticity, the rheological properties and the injectability of the cement.

[0056] An appropriate liquid phase includes one or more of the following: saline, deionized water, dilute phosphoric acid, dilute organic acids (acetic, citric, succinic acid), sodium phosphate, sodium carbonate or bicarbonate, sodium alginate, sodium bicarbonate, sodium chondroitin sulphate and/or a $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7/\text{NaH}_2\text{P}_2\text{O}_7$ aqueous solution.

[0057] Water, a $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ aqueous solution, a NaCl solution or a sodium citrate solution, are preferred. For example, a solution of 2 to 3% by weight of Na_2HPO_4 in distilled water or a 0.9% NaCl solution can be used.

[0058] The pH of the liquid phase should be between 5 to 10, preferably between 5 and 9, most preferably between 5 and 7.

[0059] Preferably, the liquid phase/solid phase (L/S) ratio is between 0.25 to 0.7 ml/g, more preferably between 0.3 to 0.6 ml/g, the most preferably 0.4 ml/g.

[0060] The setting time, which can range from 10 to 60 min, preferably 10 to 30 min, depends on the composition of the powder and liquid components, the powder-to-liquid ratio, proportion of the calcium phosphate components and the particle sizes of the powder components. The setting time of the cement is an important property of the cement. If the setting time is too fast, the surgeon does not have time to use the cement before it is hard. If the setting time is too long, the surgeon must wait until he/she can close the wound.

[0061] In a preferred embodiment, at least one of the components comprises a setting regulator, a setting accelerator or a setting retarder or both.

[0062] A very efficient way to accelerate the setting time is to have large concentrations of phosphate ions in the mixing solution. This can happen via two ways: (i) a soluble phosphate salt is added as a powder in the cement formulation. Upon contact with the mixing solution, the phosphate salt dissolves, and hence accelerates the chemical reaction using up phosphate (LeChatelier principle); (ii) a soluble phosphate salt is pre-dissolved in the mixing liquid phase. Examples of soluble phosphate salts are Na_2HPO_4 , NaH_2PO_4 , K_2HPO_4 , KH_2PO_4 , $\text{NH}_4\text{H}_2\text{PO}_4$. Typical concentrations in the mixing liquid phase are in the range of 0.05 to 1.00 M. Another way to accelerate the setting reaction is to add germs for apatite crystal growth, as the nucleation step of the setting reaction is a limiting factor. Typically, apatite crystals can be used, preferably a calcium-deficient hydroxyapatite or hydroxyapatite powder. Small amounts (a few weight percents) are sufficient to drastically reduce the setting time.

[0063] When the setting time is too short, various setting additives can be added to increase the setting time. Typical examples are compounds which inhibit the nucleation and/or growth of apatite crystals. Common examples are pyrophosphate, citrate or magnesium ions. One particularly interesting compound is calcium carbonate. The one skilled in the art would obtain the appropriate setting time with routine assays.

[0064] Preferably, a CPC according to the invention is injectable. Indeed, in recent years, the occurrence of osteoporotic fractures has dramatically increased. Considering the lack of adequate cure and the increasing number of elderly people, this trend is expected to continue. Osteoporotic fractures are often very difficult to repair, because the bone is very weak. It is therefore not possible to insert screws to hold osteosynthesis plates. A way to solve the problem is to inject a CPC into the osteoporotic bone to reinforce it. The injection of a CPC into an osteoporotic bone is only possible if the cement is well injectable.

[0065] In order to prevent any extravasation of the cement into the tissues surrounding bone, it is very important to visualise the cement. The easiest way is to increase the radio-opacity of the cement, for example by means of contrasting agents. For example, metallic powders of tantalum, titanium or tungsten can be used. It might be preferable to use liquid agents in partially bioresorbable cements, such as iodine compounds as iopamidol, iohexol and iotrolan. Preferably, barium sulphate is used.

[0066] Quite often, bone defects are not due to a traumatic event, but to a disease, e.g. bone tumour, infection, etc... In these cases, it is interesting to incorporate drugs in the cement, in particular pharmaceutically or physiologically active substances, preferably antibiotics, anti-inflammatory drugs, anti-cancer drugs, drugs against osteoporosis, peptides, and proteins such as growth factors. Owing to their structure and their dissolution property, the calcium phosphate cements are able to slowly release the active ingredients into the environment within a few days after implantation. These active ingredients can also be encapsulated in a microcapsule of a biocompatible and bioresorbable polymer of the organic component of the CPC according to the invention.

[0067] Another object of the invention is the use of a CPC according to the invention as a scaffold for tissue engineering.

[0068] The CPC according to the invention can also be employed to produce a dental or a bony implant.

[0069] A further object of the invention is the use of an injectable CPC according to the invention to fill a bony defect or fracture caused by trauma or associated with osteoporosis. This includes a surgery step but injectable CPCs according

to the invention can get to inaccessible parts of the body and are suited for minimally invasive surgery procedures that are intended to reduce damage and pain while hastening return to function. This method of treatment comprises the introduction in the bony defect or fracture through a needle of an injectable CPC according to the invention.

[0070] For example, they can be employed in percutaneous vertebroplasty. This consists of a percutaneous puncture method to stabilize and straighten vertebral collapse of the thoracic and lumbar spinal column, most often as a result of osteoporosis.

[0071] In the course of osteoporosis, a very painful vertebral collapse can occur in the region of the thoracic (TSC) and lumbar (LSC) spinal column as a result of the reduced load-bearing capacity of the skeletal frame. This results in more or less distinct deformation of the vertebrae, and even in vertebral collapse. Both cases are easily recognizable by x-ray. Even a complete vertebral collapse and distinct deformation of the entire spinal column is possible.

[0072] Under local anesthetic, or, if desired, under full narcosis, a thin puncture needle is inserted to the vertebra, e.g. under x-ray guidance. At a certain point of the vertebra (the so-called pedicle), the bone can be punctured by the needle without risk. Afterwards, fluid bone cement is injected into the vertebra via the puncture needle; after the cement hardens, the vertebra is stabilized (vertebroplasty). If the vertebra is severely deformed (e.g. in the case of a wedge-like formation), the collapsed vertebra is straightened before the cement is injected. A balloon is hereby inserted into the vertebra via the puncture needle and inflated with fluid under high pressure. Following a successful straightening, the balloon is removed and the resulting cavity is filled with bone cement (balloon-kyphoplasty).

[0073] The following examples illustrate and describe preferred embodiments of the invention.

Examples

Example 1 : preparation of poly(ϵ -caprolactone) microspheres

[0074] 1 g of poly(ϵ -caprolactone) (Tone® P787, Union Carbide SA, France) has been dissolved in 15 mL of Recaptur dichloromethane (Prolabo, France). This solution has been emulsified in an aqueous solution (1 L) of methylcellulose (Méthocel® A15LV premium EP, Colorcon, France) (0,75 g) at 4°C, under constant shaking (550 rpm), for 90 min. The resulting emulsion is then added to 1 litre of distilled water. The resulting suspension is then filtered in vacuum. The microspheres are then washed with 1 litre of distilled water and dried at room temperature for 24h.

Example 2 : preparation of poly(ϵ -caprolactone) microcapsules encapsulating water

[0075] The same process as Example 1 is used to produce microcapsules of poly(ϵ -caprolactone) encapsulating water except for adding of water in the polymer before the emulsion.

Example 3 : preparation and characterization of apatitic calcium phosphate cements according to the invention

[0076] The inorganic component consists of α -TCP.

[0077] The organic component consists of microspheres or microcapsules of poly(ϵ -caprolactone) encapsulating water.

[0078] An aqueous solution of Na_2HPO_4 (3%) is used as liquid phase.

[0079] Different cements with different liquid/powder ratios (L/P) have been prepared ($0.32 \text{ mL} \cdot \text{g}^{-1} < \text{L/P} < 0.40 \text{ mL} \cdot \text{g}^{-1}$) and different percentages of microparticles of poly(ϵ -caprolactone) from 0 to 10%.

[0080] The inorganic and organic components are mixed with the liquid phase and the mixing is placed in a cylinder-shaped mould. After 15 min, the mould is placed in a 0,9% NaCl solution at 37°C. These conditions simulate the in vivo conditions. The saline solution is changed every three days. The incubation time is one week or one month.

[0081] After the incubation period, the cylinders are taken out of moulds and assayed.

[0082] Table I summarizes the different conditions.

Table I

N°	L/P ($\text{mL} \cdot \text{g}^{-1}$)	α -TCP weight (g)	Liquid phase Volume (mL)	Microparticles (%)	Microparticles weight (g)	Incubation time
1	0.32	6.25	2	0	0	1 week
2	0.40	5.00	2	0	0	1 week
3	0.32	6.25	2	0	0	1 week
4	0.40	5.00	2	0	0	1 week
5	0.32	2.94	2	5	0.31	1 week

(continued)

N°	L/P (mL.g ⁻¹)	α -TCP weight (g)	Liquid phase Volume (mL)	Microparticles (%)	Microparticles weight (g)	Incubation time
6	0.40	7.13	3	5	0.38	1 week
7	0.32	5.94	2	5	0.31	1 month
8	0.40	6.75	3	10	0.75	1 month
9	0.32	5.63	2	10	0.63	1 month
10	0.32	2.87	1	10 (encapsulating water)	0.32	1 week

[0083] The samples are assayed by mercury porosimetry and the results are summarized in Table II.

Table II :

N°	Porosity (%)	Density (g/mL)	Diameter in average (μ m)
1	27	1.85	0.018
2	36	2.5	0.011
5	27	2.20	0.011
6	37	1.98	0.012
7	27	2.34	0.011
8	37	2.10	0.012
9	28	2.19	0.011
10	45	2.74	0.0154

Claims

1. A cement powder useful as bone cement comprising an organic component consisting of one or more biocompatible and bioresorbable polymers, and an inorganic component consisting of one or more calcium phosphate compounds.
2. A cement powder according to claim 1, wherein said biocompatible and bioresorbable polymers belong to the linear polyester family.
3. A cement powder according to claim 1 or 2, wherein said biocompatible and bioresorbable polymers are selected from the group consisting of poly-lactic acids, collagen, polyglycolic acid and polycaprolactone and their associated copolymers, polyorthoester, polyanhydride, polydioxanone, hyaluronic acid and polyhydroxybutyrate, polyphosphazenes, dendrimers and polysaccharides, and their salts and mixtures thereof.
4. A cement powder according to claim 3, wherein said biocompatible and bioresorbable polymers are selected from the group consisting of polyphosphazenes, dendrimers and polysaccharides, and their salts and mixtures thereof.
5. A cement powder according to claim 4, wherein said biocompatible and bioresorbable polymers are polyphosphazenes selected from the group consisting of poly(ethyl oxybenzoate)phosphazene (PN-EOB), poly(propyl oxybenzoate) phosphazene (PN-POB), poly[bis(sodium carboxylatophenoxy)phosphazene] (Na-PCPP), poly[bis(potassium carboxylatophenoxy) phosphazene] (K-PCPP), poly[bis(ethyl alanato)phosphazene] (PAIaP), poly[bis(carboxylatophenoxy)phosphazene] (acid-PCPP), and their salts and mixtures thereof.
6. A cement powder according to claim 4, wherein said biocompatible and bioresorbable polymers are polysaccharides selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC).

7. A cement powder according to one of claims 1 to 6, wherein said biocompatible and bioresorbable polymers are used as microparticles.
8. A cement powder according to claim 7, wherein said microparticles have a diameter between 20 and 300 μm .
9. A cement powder according to claim 7 or 8, wherein said microparticles are microspheres or microcapsules, preferably encapsulating saccharose, glucose, water, a gas as air, an antibiotic, an anti-inflammatory drug, an anti-cancer drug, a drug against osteoporosis, a growth factor or a mixture thereof.
10. A cement powder according to one of claims 1 to 9, wherein said calcium phosphate compounds are selected from the group consisting of HA, ACP, MCPH, DCPD, DCPA, CDA, α -TCP, β -TCP, TTCP, and mixtures thereof.
11. A cement powder according to claim 10, wherein said calcium phosphate compounds are selected from the group consisting of α -TCP, β -TCP, ACP, MCPH, DCPA and mixtures thereof.
12. A cement powder according to one of claims 1 to 11, wherein said calcium phosphate compounds comprise α -TCP.
13. A cement powder according to one of claims 1 to 12, wherein the amount of polymer is in the range from 0.1 to 30%, preferably 2 to 30%, of the powder total amount.
14. An apatitic calcium phosphate cement resulting from the mixing of a powder cement according to claims 1 to 13 and a liquid phase, and setting.
15. An apatitic calcium phosphate cement according to claim 14, with a macroporosity above 100 μm , preferably between 100 and 300 μm .
16. An apatitic calcium phosphate cement according to claim 14 or 15, with a compressive strength above 20 MPa, preferably 25 MPa.
17. An apatitic calcium phosphate cement according to one of claims 14 to 16, wherein the liquid phase includes one or combinations of the following solutions: saline, deionized water, dilute phosphoric acid, dilute organic acids (acetic, citric, succinic), sodium phosphate, sodium carbonate or bicarbonate, sodium alginate, sodium bicarbonate, sodium chondroitin sulphate, sodium citrate and/or a $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ aqueous solution.
18. An apatitic calcium phosphate cement according to one of claims 14 to 17, wherein the pH of the liquid phase is in the range of 5 to 10, preferably 5 to 9.
19. An apatitic calcium phosphate cement according to one of claims 14 to 18, wherein the liquid phase/powder cement (L/S) ratio is between 0.25 to 0.7 ml/g, preferably between 0.3 to 0.6 ml/g, most preferably 0.4 ml/g.
20. An apatitic calcium phosphate cement according to one of claims 14 to 19, having a setting time between 10 and 30 min.
21. An apatitic calcium phosphate cement according to one of claims 14 to 20, being injectable.
22. An apatitic calcium phosphate cement according to one of claims 14 to 21, including further a contrasting agent, preferably barium sulphate.
23. An apatitic calcium phosphate cement according to one of claims 14 to 22, comprising further one or more ingredients selected from the group of antibiotics, anti-inflammatory drugs, anti-cancer drugs, drugs against osteoporosis, growth factors.
24. Use of a CPC according to claims 14 to 23, as a bone cement.
25. Use of a CPC according to claims 14 to 23, as a scaffold for tissue engineering.
26. Use of a CPC according to claims 14 to 23, to produce a dental or bony implant.

27. Dental or bony implant consisting of a moulding of a CPC according to claims 14 to 23.

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which under Rule 45 of the European Patent Convention EP 06 29 1352 shall be considered, for the purposes of subsequent proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	100SS P.: "A NEW INJECTABLE BONE SUBSTITUTE COMBINING POLY(E-CAPROLACTONE) MICROPARTICLES WITH BIPHASIC CALCIUM PHOSPHATE GRANULES" BIOMATERIALS, vol. 22, 2001, pages 2785-2794, XP002418666 * the whole document * -----	1-27	INV. A61L24/00 A61L27/40
X	US 2004/137032 A1 (WANG FRANCIS W [US]) 15 July 2004 (2004-07-15) * paragraphs [0008] - [0010], [0023] - [0034] * * claims 1-23; examples 1,2 * -----	1-4, 6-11, 13-18, 21,23-27	
E	EP 1 712 244 A (EBI L P [US]) 18 October 2006 (2006-10-18) * the whole document * ----- -/--	1-4, 6-18,21, 23-27	
			TECHNICAL FIELDS SEARCHED (IPC)
			A61L
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search: see sheet C</p>			
Place of search		Date of completion of the search	Examiner
The Hague		14 February 2007	Derrien, Anne-Cécile
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p>			

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EPO FORM 1503 03.02 (F04C07)



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Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 06 29 1352

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	EP 1 216 718 B1 (ETHICON INC [US]) 6 October 2004 (2004-10-06) * paragraphs [0020], [0052] * -----	1-27	
A	LE RAY A-M ET AL: "Vancomycin encapsulation in biodegradable poly(E-caprolactone) microparticles for bone implantation. Influence of the formulation process on size, drug loading, in vitro release and cytocompatibility" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 24, no. 3, February 2003 (2003-02), pages 443-449, XP004390664 ISSN: 0142-9612 * the whole document *	1-27	
			TECHNICAL FIELDS SEARCHED (IPC)
D,A	WO 2006/030054 A (UNIV CATALUNYA POLITECNICA [ES]; GINEBRA MOLINS MARIA PAU [ES]; PLANEL) 23 March 2006 (2006-03-23) * the whole document *	1-27	
A	WO 2004/091435 A2 (ETEX CORP [US]; ROSENBERG ARON D [US]; GILLES DE PELICHY LAURENT D [US]) 28 October 2004 (2004-10-28) * the whole document *	1-27	



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SHEET C**

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Although claims 24-26 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 06 29 1352

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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14-02-2007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004137032 A1	15-07-2004	NONE	
EP 1712244 A	18-10-2006	US 2006233851 A1	19-10-2006
EP 1216718 B1	06-10-2004	AU 762855 B2	10-07-2003
		CA 2365376 A1	21-06-2002
		DE 60106183 D1	11-11-2004
		DE 60106183 T2	13-10-2005
		EP 1216718 A1	26-06-2002
		JP 2002320631 A	05-11-2002
		US 2006067967 A1	30-03-2006
		US 2003147935 A1	07-08-2003
WO 2006030054 A	23-03-2006	ES 2246726 A1	16-02-2006
WO 2004091435 A2	28-10-2004	AU 2004229502 A1	28-10-2004
		CA 2521623 A1	28-10-2004
		EP 1615596 A2	18-01-2006
		JP 2006522670 T	05-10-2006
		KR 20050123154 A	29-12-2005

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2006030054 A [0014]

Non-patent literature cited in the description

- **LEGEROS et al.** Apatitic Calcium Phosphates : Possible Restorative Materials. *J Dent Res*, 1982, vol. 61, 343 [0005]